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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: ACETOCHLOR - Qualitative Risk assessment from a Rat 2-Year Chronic/Oncogenicity Study. Caswell No. -3B

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SUMMARY:

Acetochlor was fed to male and female Sprague-Dawley rats at doses of 0, 40, 200, and 1000 ppm in a 107 week chronic toxicity/oncogenicity study.

For the female rat there were no survival problems. The incidence of nose papillary adenomas was significantly increased in the 1000 ppm dose group compared to controls and there was a significant dose-related trend. There was a significant dose related trend for thyroid follicular cell adenomas and/or carcinomas combined.

For the male rat there were no survival problems. The incidence of nose papillary adenomas was significantly increased in the 1000 ppm dose group compared to controls and there was a significant dose-related trend.

BACKGROUND:

This is a repeat of a previous chronic/oncogenicity study in the rat. Acetochlor (96.1 % purity) was fed to male and female Sprague-Dawley rats at doses of 0, 40, 200, and 1000 ppm in a 107 week chronic toxicity/oncogenicity study. Approximately 10 animals of each sex were sacrificed after 52 weeks of continuous dosing in each dose group. The study was conducted by the Monsanto Environmental Health Lab for Monsanto Company. The report number was MSL-6119, EPA Accesion Number 400770601. Data was extracted from a final report dated September 25, 1986. Test animals were assigned randomly to the following groups:

Table 1. Experimental Design for Rat Chronic Study

	Time of Sacrifice (weeks)			
Dose	Total Number		52	
(ppm)	Male	Female	Male	Female
Control	70	70	10	10
40	70	70	10	10
200	70	70	10	10
1000	70	70	10	10

SURVIVAL ANALYSIS:

For the female rat there were no statistically significant results detected in mortality for either pair-wise comparisons of differences between the treated and the control or a linear trend with dose (Table 2).

For the male rat there were no statistically significant results detected in mortality for either pair-wise comparisons of differences between the treated and the control, or a linear trend with dose (Table 3).

Test for mortality were made using the Thomas, Breslow, and Gart procedure.

TABLE 2. ACETOCHLOR, ALBINO RAT Study-- FEMALE Mortality Rates+ and Cox or Generalized K/W Test Results

	WEEK					
DOSE(PPM)	1-26	27-54	54a	55-78	79-107a	TOTAL
0.000	1/70 (1)	0/69 (0)	10/10	10/59 (17)	25/49 (51)	36/60 (60)
40.000	0/70 (0)	1/70 (1)	10/10	9/59 (15)	24/50 (48)	34/60 (57)
200.000	2/70 (3)	1/68 (1)	10/10	12/57 (21)	19/45 (42)	34/60 (57)
1000.000	0/70 (0)	3/70 (4)	10/10	5/57 (9)	22/52 (42)	30/60 (50)

TABLE 3. ACETOCHLOR, ALBINO RAT Study-- MALE Mortality Rates+ and Cox or Generalized K/W Test Results

	WEEK					
DOSE(PPM)	1-26	27-54	54a	55-78	79-107a	TOTAL
0.000	0/70 (0)	1/70 (1)	10/10	4/59 (7)	27/55 (49)	32/60 (53)
40.000	2/70 (3)	2/68 (3)	10/10	3/56 (5)	29/53 (55)	36/60 (60)
200.000	0/70 (0)	1/70 (1)	10/10	11/59 (19)	25/48 (52)	37/60 (62)
1000.000	1/70 (1)	0/69 (0)	10/10	7/59 (12)	27/52 (52)	35/60 (58)

\+ Number of animals that died during the interval/Number of animals alive at the beginning of the interval.
( ) Per cent

a Interim sacrifice was conducted at 54 weeks. Final sacrifice occurred at week 107.

Note: Time intervals were selected for display purposes only. Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

TUMOR ANALYSIS:

In the absence of any mortality differences for either sex of rats, Fisher's exact test was used to test for pair-wise differences between control and treated rats. The Cochran-Armitage trend was used to test for increasing incidence with increasing dose levels.

In the female rats, there was a significant linear trend for combined thyroid carcinomas and adenomas ($p = .0457$, Table 6). There were no other significant pair-wise differences or linear trends for thyroid adenomas or thyroid carcinomas. The incidence of papillary adenomas of the nose in the 1000 ppm group was significantly increased ($p < .0001$, Table 7) compared to controls and there was a significant dose-related trend ($p < .0001$).

In the male rats, there were no significant pair-wise differences or linear trends for thyroid adenomas (Table 8). There were no thyroid carcinomas. The incidence of papillary adenomas of the nose in the 1000 ppm group was significantly increased ($p = .0010$, Table 9) compared to controls and there was a significant dose-related trend ($p < .0001$).

TABLE 4. ACETOCHLOR ALBINO RAT Study-- FEMALE Thyroid Follicular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE	0.000	40.000	200.000	1000.000
ADENOMA	1/39 a (2.6)	2/44 a (4.5)	2/36 (5.6)	4/46 (8.7)
	p= 0.1124	p= 0.4015	p= 0.3639	p= 0.1940
CARCINOMA	0/30 (0.0)	0/35 (0.0)	0/28 (0.0)	1/36 b (2.8)
	p= 0.0537	p= 1.0000	p= 1.0000	p= 0.5455
ADENOMA CARCINOMA	1/39 (2.6)	2/44 (4.5)	2/36 (5.6)	5/46 (10.9)
	p= 0.0457 *	p= 0.4015	p= 0.3639	p= 0.1222

a First Adenoma observed at 90 weeks in dose 0 and 40 ppm.
b First Carcinoma observed at 100 weeks in dose 1000 ppm.

TABLE 5. ACETOCHLOR ALBINO RAT Study-- FEMALE Nose Papillary Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE	0.000	40.000	200.000	1000.000
ADENOMA	0/69 (0.0)	0/69 (0.0)	0/67 (0.0)	19/68 c (27.9)
	p< 0.0001 **	p= 1.0000	p= 1.0000	p< 0.0001 **

+ Number of tumor bearing animals/Number of animals at risk. (Excluding animals that died before the observation of the first tumor or animals not examined).
( ) Per cent

c First Adenoma observed at 54 weeks in dose 1000 ppm.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

TABLE 6. ACETOCHLOR, ALBINO RAT Study-- MALE Thyroid Follicular Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE	0.000	40.000	200.000	1000.000
ADENOMA	1/56 (1.8)	1/53 (1.9)	1/54 a (1.9)	2/54 (3.7)
	P= 0.2208	p= 0.5042	p= 0.5044	p= 0.3713

a First Adenoma observed at 75 weeks in dose 1000 ppm..
No Carcinomas occurred in male rats.

TABLE 7. ACETOCHLOR, ALBINO RAT Study-- MALE Nose Papillary Tumor Rates+ and Cochran-Armitage Trend Test and Fisher's Exact Test Results

DOSE	0.000	40.000	200.000	1000.000
ADENOMA	1/58 (1.7)	0/54 (0.0)	0/58 (0.0)	12/59 (20.3)
	P< 0.0001 **	p= 0.5179	p= 0.5000	p= 0.0010 **

\+ Number of tumor bearing animals/Number of animals at risk. (Excluding animals that died before the observation of the first tumor or animals not examined).
( ) Per cent

a First Adenoma observed at 67 weeks in dose 1000 ppm.

Note: Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at Dose level. * denotes $p < 0.05$ and ** denotes $p < 0.01$

REFERENCES:

Thomas, D G, N Breslow, and J J Gart, Trend and Homogeneity Analyses of Proportions and Life Table Data, Computers and Biomedical Research 10, 373-381, 1977.

Cochran, W.G. Some Methods for Strengthening the Common X^2 Test. Biometrics 10, 417-451, 1954.

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increasing linear trend with dose. The incidence of malignant mammary tumors and all mammary tumors combined was significantly increased in the 1000 ppm dose group compared to controls and there was a significant increasing dose-related trend for both analyses. The 3 ppm dose group was significantly increased compared to control for malignant mammary tumors.